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Characterisation of an ATP receptor mediating mitogenesis in vascular smooth muscle cells.

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Adenosine triphosphate (ATP), a co-transmitter in sympathetic nerves and released from platelets, has recently been shown to stimulate growth of vascular smooth muscle cells. It might therefore contribute to the development of vascular hypertrophy seen in hypertension and atherosclerosis. We aimed at characterising the receptor mediating this mitogenic effect in rat aorta smooth muscle cells. The potency of agonists indicates a P2 purinoceptor since ATP > or = ADP >> AMP, adenosine. The P2x-receptor subtype, which is responsible for ATP induced vasoconstriction in rat aorta, does not mediate the mitogenic effect since alpha, beta-methyleneATP had no effect and beta, gamma-methyleneATP had lower potency than ATP. The P2Y-receptor subtype was excluded since the selective agonist 2-methylthioATP had weak effect with lower potency than ATP. When we studied the involvement of other nucleotides similar effects were seen of the purines ATP, GTP and ITP; also the pyrimidine UTP had powerful mitogenic effects (Emax = 52% of ATP) with similar potency. Nucleotides with fewer phosphate groups showed a stepwise fall in mitogenic effect. This indicates involvement of a nucleotide-receptor (P2U). Ap4A were of equal potency and effect as ATP. There was strong correlation between the mitogenic effects of the nucleotides and analogues with both 45Ca(2+)-influx and inositol phosphate (IP) production, indicating that they may participate in mediating the mitogenic response. This is the first study describing the potencies for the mitogenic effects of the selective ATP-analogues and other nucleotides in vascular smooth muscle cells. The receptor characterisation indicates a nucleotide-receptor similar to the receptor which stimulates 45Ca(2+)-influx and inositol phosphate-formation in rat aorta smooth muscle cells. Substances related to ATP such as GTP, ITP, UTP and Ap4A which also can be released extracellularly in vivo stimulate mitogenesis of rat aorta smooth muscle cells through the same receptor.

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